

REMARKS/ARGUMENTS

Claims 1-12 and 19-23 are active. Claims 13-18 were previously withdrawn from consideration and have now been cancelled. Claim 1 and its dependents have been revised to specify that the C₁-C₁₈-alkyl esters of (meth)acrylic acid component is ethylacrylate. The weight % of 60 to 35% for this ingredient finds support in original claim 1 (upper 60% value) and claim 4 (lower 35% value) and at the top of page 10 of the specification. The 35-60% range of ethylacrylate in claims 3, 8 and 21 finds support in B and C of Table 5 on page 32 of the specification. The “no transition metal complexes” limitation has been removed from claim 1, but now appears in dependent claim 5. Claims 6-7 have been revised to track the disclosure at page 14, lines 1-13. Claim 8 has been revised to include the limitations of claim 1 from which it had depended as well as to refer to pH-sensitive polymers containing ethylacrylate. Other consistent revisions have been made to the remaining claims. No new matter has been added. Favorable consideration of this amendment and allowance of the application is respectfully requested.

The Applicants thank Examiner Bernshsteyn for the helpful and courteous interview of November 20, 2008 and the helpful discussion on February 12, 2009. It was suggested that the Applicants consider directing the claims to pH-sensitive polymers containing ethylacrylate since the experimental data of record, e.g., in Tables 1, 4, and 5, demonstrate the superior properties of such pH-sensitive polymers compared to other types of polymers. Incorporation of the limitations of claim 8 into claim 1 were also discussed as a possible means to avoid the prior art which does not suggest copolymers containing or combined with pharmaceutical agents usable for therapeutic purposes.

Restriction/Election

Applicants previously elected with traverse, Group I, Claims 1-12, directed to a pH-sensitive polymer and a method of making it. Claims 13-18 were previously withdrawn from consideration and have now been cancelled. The Restriction Requirement has been made FINAL.

Rejection—35 U.S.C. §103

Claims 1-12 and 19-20 stand rejected under 35 U.S.C. 103(a) as being obvious over Haddleton et al., U.S. Patent 5,804,632, in view of Rehmer, et al., U.S. Patent No. 6,225,401. In view of the amendments above, as well as the arguments of record, the Applicants respectfully submit that this rejection no longer applies. The prior art provides no suggestion to select ethylacrylate in an amount between 35-60 wt.% (or 35-50 wt.%) in combination with methylacrylic acid in an amount ranging from 25-65 wt.% to provide a pH-sensitive polymer required by the present claims. Furthermore, the prior cannot provide a reasonable expectation of success for the superior pH-sensitivity of the claimed polymers because it did not suggest or provide a reasonable expectation of success for the therapeutic and biological properties of copolymers which “brings about at least 60% haemolysis at pH 5.5, and less than 5% haemolysis at pH 7.4, at a concentration of 150 µg/ml in a cytotoxicity test with human red blood cells”.

The pH-sensitivity of the claimed polymers is not inherent to the genus of acrylamide or acrylic acid based copolymers of the prior art as shown by the comparative examples of copolymers Tables 1-5 in the specification (reproduced below, copolymers B and C correspond to the claimed invention, the other copolymers do not). The prior art also provides no motivation for selecting the subclass of copolymers required by the invention to

have particular compositions, e.g., 35-60 wt%. ethylacrylate, and particular well characterized functional properties--e.g., pH-sensitivity that brings about at least 60% haemolysis at pH 5.5, and less than 5% haemolysis at pH 7.4, at a concentration of 150 µg/ml in a cytotoxicity test with human red blood cells; or the other functional characteristics described in claims 4 and 5. The Examiner's attention is directed to these tables reproduced below. Table 1 shows the composition of polymers B and C (according to the invention) and A, D, E, L-100, L-100-55 and S-100 which fall outside of the claims. Table 4 shows that polymers B and C have the pH-sensitivity required by the claims, but that the other comparative polymers do not.

Table 1

Copolymer	Methacrylic acid [wt %]	Methyl methacrylate [wt %]	Ethyl acrylate [wt %]	Methyl acrylate [wt %]	Mw × 10 ³ [mol/g]	pH range in which the copolymer precipitates
A	50	50	-	-	25	3.8 - 4.5
B	50		50		25	4.7 - 5.1
C	30	-	35	35	25	5.0 - 5.6
D	30	70	-	-	25	4.8 - 5.3
E	10	45	-	45	25	4.5 - 7.0
L-100	50	50	-	-	100	3.7 - 4.3
L-100-55	50	-	50	-	250	4.6 - 5.0
S-100	30	70	-	-	100	4.7 - 5.2

Table 2

Copolymer	Mw × 10 ³ [mol/g]	Haemolytic activity [%] at pH 7.4 with a copolymer concentration in [µg/ml]				
		150	250	500	2 500	10 000
A	25	< 5	< 5	< 5	< 5	< 5
B	25	< 5	5	8	25	100
C	25	< 5	< 5	5	100	100
D	25	< 5	< 5	< 5	100	100
E	25	< 5	< 5	< 5	12	20
L-100	100	< 5	< 5	< 5	< 5	< 5
L-100-55	250	< 5	< 5	< 5	< 5	30
S-100	100	< 5	< 5	< 5	< 5	< 5

Table 3

Copolymer	pH	Haemolytic activity [%] at a copolymer concentration in [$\mu\text{g/ml}$]				
		25	50	100	150	250
B	5,0	10	80	80	80	80
B	5,5	50	90	95	90	90
L-100-55	5,0	< 5	80	80	80	80
L-100-55	5,5	5	55	75	90	90
C	5,0	< 5	< 5	10	60	80
C	5,5	5	50	80	85	85

Table 4

Copolymer	Mw $\times 10^3$ [mol/g]	Haemolytic activity [%] with a copolymer concentration of 150 [$\mu\text{g/ml}$]				
		pH 5.5	pH 6.0	pH 6.5	pH 7.0	pH 7.5
A	25	< 5	< 5	< 5	< 5	< 5
B	25	80	55	< 5	< 5	< 5
C	25	90	55	< 5	< 5	< 5
D	25	< 5	< 5	< 5	< 5	< 5
E	25	< 5	< 5	< 5	< 5	< 5
L-100	100	< 5	< 5	< 5	< 5	< 5
L-100-55	250	95	80	< 5	< 5	< 5
S-100	100	< 5	< 5	< 5	< 5	< 5

Table 5

Copolymer	MAA	MMA	EA	MA	MTT test % cell survival		LDH test % LDH released	
					0.03125 [mg/ml]	0.5 [mg/ml]	0.03125 [mg/ml]	0.5 [mg/ml]
A	50	50	-	-	90	100	< 5	< 5
B	50		50		30	20	35	40
C	30	-	35	35	100	80	< 5	15
D	30	70	-	-	100	100	< 5	< 5
E	10	45	-	45	100	< 5	< 5	40

MAA = [wt %] methacrylic acid
MMA = [wt %] methyl methacrylate
EA = [wt %] ethyl acrylate
MA = [wt %] methyl acrylate

As shown above, the copolymers produced using ethylacrylate and selected to have the biochemical properties (e.g., pH-sensitivity) of the invention exhibit properties not suggested by the prior art and not inherent to other types of similar copolymers.

Furthermore, these superior biochemical properties are further reflected by the invention as described by claim 8. This claim merges limitations from prior independent claim 1 and requires that the pH-sensitive polymers contain a therapeutic agent. The prior art does not describe or suggest such a pH-sensitive copolymer capable of exhibiting a pharmacological effect.

Accordingly, in view of these amendments and the arguments above, this rejection can no longer be sustained.

CONCLUSION

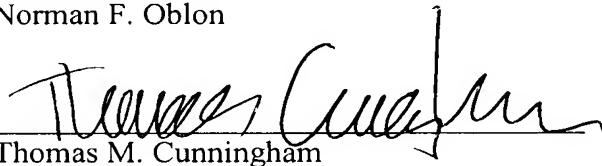
This application presents allowable subject matter and the Examiner is respectfully requested to pass it to issue. The Examiner is kindly invited to contact the undersigned should a further discussion of the issues or claims be helpful.

Respectfully submitted,

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